Carcinoid tumour of the gall bladder: two case reports and a review of published works

D J Deehan, S D Heys, N Kernohan, O Eremin

Abstract
This paper reports on two patients with carcinoid tumours of the gall bladder who presented to the Aberdeen hospitals during the period 1970 to 1990 and reviews all previously reported cases in published works. (Gut 1993; 34: 1274–1276)

The carcinoid tumour or argentaffinoma originates from the Kulchitsky cell, which is believed to be derived from the neuroendocrine epiblast tissue. This migrates during embryogenesis to various endodermal or mesodermal tissue.1 Carcinoid tumours are capable of secreting a number of polypeptide substances and also decarboxylating amine precursors in preparation for secretion for example, histamine, serotonin, 5-hydroxytryptamine.2,3 They all share common cytochemical, ultrastructural, and biosynthetic properties.4

The carcinoid tumour may arise from the appendix (35%), small bowel (25%), colon and rectum (19%), oesophagus and stomach (2%), and lungs and bronchi (14%).5,6 In the small intestine as many as 25% of cases occur as multiple localised tumours presumably because of the large number of progenitor cells in the normal tissues.1 Carcinoids arising in the biliary tract represent 0–2–2% of all carcinoid tumours arising in the gastrointestinal tract.7 Twenty seven cases of primary carcinoid tumours of the gall bladder have been reported to date and a further 12 have been described originating from the bile ducts.7

Case reports

CASE 1
A 51 year old woman presented with a two month history of right hypochondrial, colicky pain, radiating to her back, associated with fat intolerance. Pre-operative imaging investigations showed cholelithiasis and cholecystectomy was subsequently performed. Pathological examination of the gall bladder showed chronic cholecystitis and a carcinoid tumour, 2.6 mm in diameter, at the gall bladder neck (Fig 1). The tumour affected the mucosa and had infiltrated into the muscularis mucosa but had been completely excised. Histologically, it was composed of trabeculae, cords, and nests of banal polygonal cells. The tumour cells had round or oval nuclei with granular chromatin and small, occasionally multiple, nucleoli. No mitotic figures were identified and the cytoplasm was eosinophilic. The tumour cells were positive for cytokeratin (CAM 5-2), neuron specific enolase, chromogranin, and S-100 protein (Fig 1+ Inset). This patient is alive and well six months later.

CASE 2
A 33 year old woman presented with a six month history of right hypochondrial pain. Radiological investigations suggested cholelithiasis and a cholecystectomy was performed. The gall bladder showed features of chronic cholecystitis but also contained a firm nodule in its wall adjacent to Hartmann’s pouch. The nodule was a carcinoid tumour, 7 mm in diameter, composed of nests and trabeculae of banal cells with a similar morphological and immunohistochemical

Figure 1: Carcinoid tumour discovered as an incidental finding in a cholecystectomy specimen. The tumour cells occupy the gall bladder mucosa and permeate the muscularis. Inset: the tumour cells display positive nuclear and cytoplasmic staining for S-100 protein.

Figure 2: Carcinoid recognised macroscopically after cholecystectomy. The tumour extends to a surgical resection margin. Inset: the tumour cells are strongly positive for chromogranin.
Carcinoid tumour

profile as shown in the previous case (Fig 2+ Inset). The tumour infiltrated into the mucosal submucosa, extensively, penetrated the muscularis and extended into adjacent adipose tissue and to one of the resection margins. Tumour cells were noted encircling small veins and arteries but there was no evidence of vascular invasion. This patient had been followed up for 15 years and is alive and well.

Discussion

The carcinoid tumour is a relatively rare type of endocrine tumour, which arises principally in the gastrointestinal tract. It comprises less than 2% of all tumour types arising in the gastrointestinal tract. Different histological types of carcinoid tumour have been described. The typical carcinoid tumour has a bright yellow macroscopic appearance and histologically comprises cell nests, cords, and trabeculae of uniform polygonal cell set in fibroconnective tissue stroma. The tumour cells have medium sized nuclei and have granular eosinophilic cytoplasm, with inconspicuous mitotic activity. The carcinoid cells stain for the neuroendocrine specific markers, neuron specific enolase and S-100, as in both of our cases. This suggests that the tumour develops by malignant transformation of mucosal neuroendocrine cells or from undifferentiated stem cells. The characteristic ability of the midgut derived carcinoid tumours to convert ammoniacal silver to metallic silver is due to their intracytoplasmic serotonin content. The variant forms of carcinoid tumours include, the goblet cell carcinoma of the gastrointestinal tract and atypical carcinoid tumour of the lung, both of which behave more aggressively than the classic form.

All the variants possess metastatic potential, however, which is not only dependent on the site of origin but also the size of the primary lesion and its depth of invasion. The bland cytological morphology does not allow a prediction of metastatic potential to be made from histological appearances.

Primary gall bladder and biliary duct system carcinoids comprise less than 1% of all carcinoid tumours arising from any tissue or organ in the body. The first case of primary carcinoid tumour of the gall bladder was reported by Joel in 1929, and since then a further 24 cases have been described. (Tables I and II). From the published data and our two patients, the age at presentation has ranged from 26–79 years (median: 64 years). There were 17 women and eight men, two further case reports did not give details of the patient’s sex. Figure 3 outlines the incidence v age for each sex. The mode of presentation has varied considerably, but most cases (16) were detected coincidentally in patients presenting with acute or chronic cholecystitis secondary to cholelithiasis. The tumours were usually identified by routine histological examination of the gall bladder after cholecystectomy. The size or proximity of the tumour to the hepatic ducts has been responsible for mechanical obstruction and presentation as obstructive jaundice. Only two of the reported gall bladder carcinoids presented in this manner, whereas, one half of the documented carcinoid tumours of the extra hepatic ducts presented with obstructive jaundice. Furthermore, the carcinoid syndrome has been found in only two patients, both of whom had disseminated disease.

Pre-operative diagnosis of carcinoid tumour of the gall bladder is difficult, mainly because of its small size and limitations in the resolution of the currently available radiological imaging techniques. Nevertheless, 11 of 27 patients with gall bladder carcinoid tumours (including our two cases) had a pre-operative ultrasound examination. In seven of these patients a mass consistent with a carcinoid tumour was identified. Most of the tumours were undetected before surgery, however, and in the absence of other associated phenomena, such as the carcinoid syndrome (two cases), pre-operative diagnosis was not made.

The surgical treatment undertaken in these patients has varied, ranging from simple cholecystectomy to more extensive surgical resections, including regional lymph node clearances and hepatic lobectomy. Cholecystectomy alone was performed in 14 patients and a further four patients had, in addition to cholecystectomy, a regional lymph node clearance. Four other patients had cholecystectomy combined with hepatic lobectomy, for locally advanced disease. The role of radiotherapy and chemotherapy in the management of these patients is unclear because it is believed that, in general, carcinoid tumours are insensitive to radiotherapy. Chemotherapy has been reported to be of palliative value in carcinoid tumours arising in other sites. Radiotherapy has been used in one

### TABLE I Clinical data on women with carcinoid tumours

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Treatment</th>
<th>Local recurrence</th>
<th>Metastases</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>66</td>
<td>a</td>
<td>No</td>
<td>No</td>
<td>Died after two months</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>b</td>
<td>Yes</td>
<td>Yes</td>
<td>Died after four months</td>
</tr>
<tr>
<td>10</td>
<td>77</td>
<td>d</td>
<td>No</td>
<td>No</td>
<td>Died after two months</td>
</tr>
<tr>
<td>11</td>
<td>65</td>
<td>c</td>
<td>No</td>
<td>Yes</td>
<td>Well at 12 months</td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>x</td>
<td>Yes</td>
<td>x</td>
<td>Found after death</td>
</tr>
<tr>
<td>13</td>
<td>59</td>
<td>a</td>
<td>Yes</td>
<td>x</td>
<td>Died after five months of septicaemia</td>
</tr>
<tr>
<td>14</td>
<td>64</td>
<td>b</td>
<td>Yes</td>
<td>x</td>
<td>Iatrogenic (developed carcinoid syndrome)</td>
</tr>
<tr>
<td>15</td>
<td>79</td>
<td>a</td>
<td>No</td>
<td>No</td>
<td>Well at six months</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>a</td>
<td>No</td>
<td>No</td>
<td>Well at 18 months</td>
</tr>
<tr>
<td>16</td>
<td>62</td>
<td>a</td>
<td>No</td>
<td>No</td>
<td>Died after five months of septicaemia</td>
</tr>
<tr>
<td>17</td>
<td>62</td>
<td>a</td>
<td>Yes</td>
<td>Yes</td>
<td>Died after two months</td>
</tr>
<tr>
<td>18</td>
<td>51</td>
<td>c</td>
<td>X</td>
<td>x</td>
<td>Died immediately postoperatively</td>
</tr>
<tr>
<td>19</td>
<td>77</td>
<td>a</td>
<td>No</td>
<td>No</td>
<td>Died at 17 months</td>
</tr>
<tr>
<td>19</td>
<td>76</td>
<td>a</td>
<td>No</td>
<td>No</td>
<td>Died after &gt; seven years</td>
</tr>
<tr>
<td>This study a</td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
<td>Died at 15 years</td>
</tr>
<tr>
<td>This study b</td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
<td>Died after six months</td>
</tr>
</tbody>
</table>

a=cholecystectomy; b=cholecystectomy + regional node clearance; c=cholecystectomy + hepatic lobectomy; d=cholecystectomy + omentectomy; e=chemotherapy; f=radiotherapy; x=not stated.

### TABLE II Clinical data on men with carcinoid tumours

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Treatment</th>
<th>Local recurrence</th>
<th>Metastases</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>68</td>
<td>f</td>
<td>x</td>
<td>Yes</td>
<td>Died after eight months</td>
</tr>
<tr>
<td>21</td>
<td>56</td>
<td>a</td>
<td>No</td>
<td>No</td>
<td>Well at one year</td>
</tr>
<tr>
<td>22</td>
<td>45</td>
<td>a</td>
<td>No</td>
<td>No</td>
<td>Well at five years</td>
</tr>
<tr>
<td>23</td>
<td>26</td>
<td>a+e+f</td>
<td>Yes</td>
<td>Yes</td>
<td>Died after 11 months</td>
</tr>
<tr>
<td>24</td>
<td>77</td>
<td>c</td>
<td>Yes</td>
<td>x</td>
<td>Died after five months of septicaemia</td>
</tr>
<tr>
<td>25</td>
<td>51</td>
<td>a</td>
<td>No</td>
<td>No</td>
<td>Died after 17 months</td>
</tr>
<tr>
<td>26</td>
<td>71</td>
<td>e</td>
<td>No</td>
<td>Yes</td>
<td>Died after six months</td>
</tr>
<tr>
<td>27</td>
<td>71</td>
<td>e</td>
<td>Yes</td>
<td>x</td>
<td>Died after 35 months (developed carcinoid syndrome)</td>
</tr>
<tr>
<td>5</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>No</td>
<td>x</td>
</tr>
<tr>
<td>2</td>
<td>x</td>
<td>a</td>
<td>No</td>
<td>No</td>
<td>Well after seven years</td>
</tr>
</tbody>
</table>

a=cholecystectomy; b=cholecystectomy + regional node clearance; c=cholecystectomy + hepatic lobectomy; d=cholecystectomy + omentectomy; e=chemotherapy; f=radiotherapy; x=not stated; sex of patients in reference 2 and 5 not stated.
who received either chemotherapy or radiotherapy or both were dead within 35 months from the time of the original diagnosis.

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